## REMARKS

The Final Office Action of December 8, 2004, has been received and reviewed.

Claims 1-27 are currently pending and under consideration in the above-referenced application, each standing rejected.

Reconsideration of the above-referenced application is respectfully requested.

### Rejections Under 35 U.S.C. § 102

Each of claims 1-9, 11-13, 15, and 21 stands rejected under 35 U.S.C. § 102(b). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single reference which qualifies as prior art under 35 U.S.C. § 102. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

With respect to determining whether or not a reference inherently discloses a claimed feature, M.P.E.P. § 2112 provides:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) . . . 'To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill . . .'' *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1991).

Packard '97 or Packard '98

Claims 1-9, 13, 15, and 21 have been rejected under 35 U.S.C. § 102(b) for reciting subject matter which is purportedly anticipated by the subject matter described in Packard, J. Phys. Chem. B., 101:5070-5074 (1997) (hereinafter "Packard '97") or by the subject matter described in Packard, J. Phys. Chem. B., 102:752-752 (1998) (hereinafter "Packard '98").

Packard '97 and Packard '98 both disclose that the nature of interaction between two fluorescent molecules may be relatively easily determined by careful spectral analysis.

Packard '97 and Packard '98 disclose techniques for designing biomolecular substrates in which fluorescence resonance energy transfer (FRET) may be optimized as the core molecular backbones of such substrates are cleaved, lysed, or severed. Such techniques include evaluating the source of quenching between a pair of fluorescent dye molecules (*e.g.*, distinguishing between FRET and ground state interactions) (Packard '97). Such techniques may also include tailoring the backbone substrate (*i.e.*, NorFES) to improve dimer formation between the two dyes of a biomolecular substrate.

Neither Packard '97 nor Packard '98 describes, or anticipates, a biomolecular substrate that includes a core molecular backbone, as well as first and second dyes that form a dimer prior to covalent modification (*e.g.*, addition of chemical groups such as phosphates, sugars, and lipids; *see, e.g.*, page 4, lines 17-19) to the core molecular backbone and dissociate from one another when the core molecular backbone is covalently modified, as required of the biomolecular substrate of independent claim 1 and for use in the method of independent claim 15. Instead, the descriptions of Packard '97 and Packard '98 are limited to biomolecular substrates that include a core molecular substrate (NorFES or a derivative thereof) that is cleaved by serine protease elastase.

Therefore, neither Packard '97 nor Packard '98 anticipates each and every element of either independent claim 1 or independent claim 15, as would be required to maintain the 35 U.S.C. § 102(b) rejections of these claims.

Claims 2-9 and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

**Rejections Under 35 U.S.C. § 103(a)**

Each of claims 1-27 has apparently been rejected under 35 U.S.C. § 103(a).

The standard for establishing and maintaining a rejection under 35 U.S.C. § 103(a) is set forth in M.P.E.P. § 706.02(j), which provides:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Lee in View of Packard '98 or de Silva

Claims 1-9, 13, 15, and 21 have apparently been rejected under 35 U.S.C. § 103(a) (as the teachings of Packard '98 or de Silva are relied upon for meeting at least one claim limitation; M.P.E.P. § 2131.01) for reciting subject matter which is allegedly unpatentable over the subject matter taught in K. B. Lee et al., "A New approach to Assay Endo-Type Carbohydrases: Bifluorescent-Labeled Substrates for Glycoamidases and Ceramide Glycanases," Analytical Biochemistry, 01 September 1995, Vol. 230, No. 1, Pages 31-36 (hereinafter "Lee"), in view of the subject matter taught in Packard '98 or the teachings of A.P. de Silva, et al., Signal Recognition Events with Fluorescent Sensors and Switches, Chem. Rev. 97:1515-1566 (1997) (hereinafter "de Silva").

The teachings of Lee, Packard '98, and de Silva are limited to biomolecular substrates that include dye dimers that dissociate when the substrate backbones thereof are severed, as well as assay methods that involve use of such biomolecular substrates. None of these references teaches a biomolecular substrate with a dye dimer that dissociates when the substrate backbone thereof is covalently modified, or use of such a biomolecular substrate, as required by independent claims 1 and 15, respectively.

Moreover, it is not inherent that non-FRET mechanisms are responsible for quenching in FRET-quenched dye dimers. Further, the principles that are used to design an optimal FRET-quenched system are not the same principles used in designing an optimal, or even workable, non-FRET system. Therefore, the mere knowledge that non-FRET fluorescence

quenching is possible is not sufficient motivation for one of ordinary skill in the art to replace a FRET-quenched dye pair with a non-FRET-quenched dye pair.

Therefore, the Office has not established a *prima facie* case of obviousness against either independent claim 1 or independent claim 15 obvious. As such, under 35 U.S.C. § 103(a), both of these claims are allowable over any combination of teachings from Lee, Packard '98, and de Silva.

Claims 2-9 and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Zhang

Claims 1, 3, 5, 13, 15, and 21 are apparently rejected under 35 U.S.C. § 103(a) (as the teachings of Packard '98 or de Silva are relied upon for meeting at least one claim limitation; M.P.E.P. § 2131.01) for being directed to subject matter which is purportedly unpatentable over the subject matter taught in Z. Zhang et al., "Amylase Substrate Based on Fluorescence Energy Transfer," Analytical Chimica Acta, 17 September 1990, Vol. 236, No. 2, Pages 251-256 (hereinafter "Zhang"), in view of teachings from Packard '98 or de Silva.

Like Lee, the description of Zhang with respect to associations between fluorescent dyes on the same molecule is limited to FRET-quenching. For the same reasons set forth above, one of ordinary skill in the art would not have been motivated by the teachings of Zhang, Packard '98, or de Silva to import teachings from Packard '98 or de Silva into the system of Zhang, as has been asserted.

Moreover, the teachings of Zhang, Packard '98, and de Silva are limited to biomolecular substrates that include dye dimers that dissociate when the substrate backbones thereof are severed, as well as assay methods that involve use of such biomolecular substrates. None of these references teaches a biomolecular substrate with a dye dimer that dissociates when the substrate backbone thereof is covalently modified, or use of such a biomolecular substrate, as required by independent claims 1 and 15, respectively.

Thus, a *prima facie* case of obviousness has not been set forth against independent claim 1 or independent claim 15, as would be required to maintain the 35 U.S.C. § 103(a) rejections of these claims.

Each of claims 3, 5, and 13 is allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Meldal

Claims 1-5, 7-9, 13, 15, and 21 stand rejected under 35 U.S.C. § 103(a) (as the teachings of Packard '98 or de Silva are relied upon for meeting at least one claim limitation; M.P.E.P. § 2131.01) for being drawn to subject matter which is assertedly unpatentable over the teachings of M. Meldal et al., "Anthranilamide and Nitrotyrosine as a Donor-Acceptor Pair in Internally Quenched Fluorescent Substrates for Endopeptidases: Multicolumn Peptide Synthesis of Enzyme Substrates for Subtilisin Carlsberg and Pepsin," Analytical Biochemistry, 1991, Vol. 195, Pages 141-147 (hereinafter "Meldal"), in view of teachings from Packard '98 or de Silva.

Like Lee and Zhang, Meldal also lacks any teaching or suggestion that quenching between two fluorescent dyes may be caused by anything other than FRET. Therefore, for the reasons explained above, one of ordinary skill in the art would not have been motivated to import dye pairs that are quenched by non-FRET mechanisms, as mentioned in Packard '98 and de Silva, into the FRET-quenched system of Meldal, as has been asserted.

Moreover, none of Meldal, Packard '98, or de Silva teaches or suggests a biomolecular substrate that includes a dye dimer that dissociates when the substrate backbone thereof is covalently modified, or an assay method that employs such a biomolecular substrate, as required by independent claims 1 and 15, respectively.

Therefore, the teachings of Meldal, Packard '98, and de Silva do not support a *prima facie* case of obviousness against independent claim 1 or independent claim 15, as would be required to maintain the 35 U.S.C. § 103(a) rejections of these claims.

Claims 2-5, 7-9, and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Taliani

Claims 1, 3, 5, 7, 13, 15, and 21 are rejected under 35 U.S.C. § 103(a) (as the teachings of Packard '98 or de Silva are relied upon for meeting at least one claim limitation; M.P.E.P. § 2131.01) for being directed to subject matter which is allegedly unpatentable over the subject matter taught in M. Taliani et al., "A Continuous Assay of Hepatitis C Virus Protease Based on Resonance Energy Transfer Depsipeptide Substrates," Analytical Biochemistry 1996, Vol. 240, Pages 60-67 (hereinafter "Taliani"), in view of teachings from Packard '98 or de Silva.

Taliani also lacks any express or inherent description that quenching of the fluorescence of one of two fluorescent dyes may be caused by anything other than FRET. For the same reasons set forth above, one of ordinary skill in the art would not have been motivated by the teachings of Taliani, Packard '98, or de Silva to import teachings from Packard '98 or de Silva into the system of Taliani, as has been asserted.

Moreover, the teachings of Taliani, Packard '98, and de Silva are limited to biomolecular substrates that include dye dimers that dissociate when the substrate backbones thereof are severed, as well as assay methods that involve use of such biomolecular substrates. None of these references teaches a biomolecular substrate with a dye dimer that dissociates when the substrate backbone thereof is covalently modified, or use of such a biomolecular substrate, as required by independent claims 1 and 15, respectively.

Thus, a *prima facie* case of obviousness has not been set forth against independent claim 1 or independent claim 15, as would be required to maintain the 35 U.S.C. § 103(a) rejections of these claims.

Each of claims 3, 5, 7, and 13 is allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Zandonella

Claims 1, 3-5, 7, 12, 13, 15, and 21 stand rejected under 35 U.S.C. § 103(a) (as the teachings of Packard '98 or de Silva are relied upon for meeting at least one claim limitation; M.P.E.P. § 2131.01) for reciting subject matter which is assertedly unpatentable over the teachings of C. Zandonella et al., "Fluorogenic Alkyldiacyl Glycerols as Substrates for the Determination of Lipase Activity and Stereoselectivity," Journal of Fluorescence, 1997, Vol. 7, No. 1 (Supplement), Pages 185S-186S (hereinafter "Zandonella"), in view of the subject matter taught in Packard '98 or de Silva.

The description of Zandonella, with respect to fluorescence quenching, is also limited to FRET-quenching. Like Lee, Zhang, Meldal, and Taliani, Zandonella also lacks any teaching or suggestion that quenching between two fluorescent dyes may be caused by anything other than FRET. Therefore, for the reasons explained above, one of ordinary skill in the art would not have been motivated to import dye pairs that are quenched by non-FRET mechanisms, as mentioned in Packard '98 and de Silva, into the FRET-quenched system of Zandonella, as has been asserted.

Moreover, none of Zandonella, Packard '98, or de Silva teaches or suggests a biomolecular substrate that includes a dye dimer that dissociates when the substrate backbone thereof is covalently modified, or an assay method that employs such a biomolecular substrate, as required by independent claims 1 and 15, respectively.

Therefore, the teachings of Zandonella, Packard '98, and de Silva do not support a *prima facie* case of obviousness against independent claim 1 or independent claim 15, as would be required to maintain the 35 U.S.C. § 103(a) rejections of these claims.

Claims 3-5, 7, 12, and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Hirano

Claims 1-7, 9, 11, 13, 15, and 21 have been rejected under 35 U.S.C. § 103(a) (as the teachings of Packard '98 or de Silva are relied upon for meeting at least one claim limitation; M.P.E.P. § 2131.01) for being drawn to subject matter which is purportedly unpatentable over the subject matter disclosed in Japanese patent publication JP 11-56398 of Hirano et al. (hereinafter "Hirano"), in view of the teachings of Packard '98 or de Silva.

The description of Hirano is also limited to FRET-quenching between fluorescent dyes. For the same reasons set forth above, one of ordinary skill in the art would not have been motivated by the teachings of Hirano, Packard '98, or de Silva to import teachings from Packard '98 or de Silva into the system of Hirano, as has been asserted.

Moreover, the teachings of Hirano, Packard '98, and de Silva are limited to biomolecular substrates that include dye dimers that dissociate when the substrate backbones thereof are severed, as well as assay methods that involve use of such biomolecular substrates. None of these references teaches a biomolecular substrate with a dye dimer that dissociates when the substrate backbone thereof is covalently modified, or use of such a biomolecular substrate, as required by independent claims 1 and 15, respectively.

Each of claims 2-7, 9, 11, and 13 is allowable, among other reasons, for depending either directly or indirectly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Multiple References

Claims 1-27 have been rejected under 35 U.S.C. § 103(a) for reciting subject matter which is allegedly not patentable over teachings from L. J. Macala et al., "Measurement of cAMP-Dependent Protein Kinase Activity Using a Fluorescent-Labeled Kemptide," Kidney International 1998, Vol. 54, Pages 1746-1750 (hereinafter "Macala"), U.S. Patent 5,580,747 to Schultz et al. (hereinafter "Schultz"), or C. Ventura et al., "Phorbol Ester Regulation of Opioid Peptide Gene Expression in Myocardial Cells," The Journal of Biological Chemistry,

15 December 1995, Vol. 270, No. 50, Pages 30115-30120 (hereinafter "Ventura"), in view of the teachings of D K. Blumenthal, "Development and Characterization of Fluorescently-Labeled Myosin Light Chain Kinase Calmodulin-Binding Domain Peptides" Molecular and Cellular Biochemistry, 1993, Vol. 127/128, Pages 45-50 (hereinafter "Blumenthal"), U.S. Patent 5,654,419 to Mathies et al. (hereinafter "Mathies"), Hirano, Lee, Meldal, Taliani, Zandonella, or Zhang, and Packard '98 or de Silva.

It is respectfully submitted that a *prima facie* case of obviousness has not been established against any of claims 1-27 because none of Macala or Schultz or Ventura, in view of Blumenthal, Mathies, Hirano, Lee, Meldal, Taliani, Zandonella, or Zhang and, further, in view of Packard '98 or de Silva teaches or suggests each and every element of any of claims 1-27.

With respect to amended independent claims 1, 15, 23, 25, and 27, it is respectfully submitted that none of the references, taken individually or collectively, teaches or suggests a biomolecular substrate that includes first and second fluorescent dyes that form a quenched intramolecular dimer, the quenching of which is effected, at least in part, by a non-FRET mechanism.

Macala teaches the use of a single-labeled peptide substrate to measure protein kinase activity. It is not based on intramolecular ground-state interactions since it only involves one dye per peptide. The teachings of Shultz are limited to a fluorescence-based protein kinase assay that requires separation of phosphorylated and unphosphorylated substrate peptides. It merely uses fluorescence as a way to track the different forms of the peptide. Ventura teaches the use of a single-labeled fluorescent peptide substrate to measure protein kinase C activity.

None of Blumenthal, Mathies, Hirano, Lee, Meldal, Taliani, Zandonella, or Zhang teaches or suggests that anything other than non-FRET-quenching may occur.

Packard '98 and de Silva mention dye dimers in which non-FRET quenching may occur, but does not teach or suggest a biomolecular substrate in which such a dimer may dissociate when a substrate backbone thereof is covalently modified.

It is respectfully submitted that none of these references nor the knowledge that was generally available to one of ordinary skill in the art as of the earliest priority date for the above-referenced application would have motivated one of ordinary skill in the art to pick and

choose teachings from the references in the manner that has been asserted. Specifically, one of ordinary skill in the art would not have been motivated to pick a covalently modifiable substrate from a single-dye assay system (in which there is no dye-to-dye quenching interaction) and add a pair of fluorescent dyes that dissociate from one another upon covalent modification of the substrate to reduce non-FRET quenching between the dyes. As demonstrated by Packard '98, such picking and choosing would have constituted mere conjecture and would have required an undue level of experimentation to provide a useful, enabled substrate or assay method.

Moreover, the Office has not provided any reasoning to support the notion that one of ordinary skill in the art would have been motivated to combine the reference teachings in the manner that has been asserted.

In view of the foregoing, it is respectfully submitted that the only source of motivation to combine the teachings of the references in the manner that has been asserted would have been improper reliance upon the subject matter disclosed and claimed in the above-referenced application.

Withdrawal of the 35 U.S.C. § 103(a) rejections of claims 1-27 is, accordingly, respectfully requested.

## CONCLUSION

It is respectfully submitted that each of claims 1-27 is allowable. An early notice of the allowability of each of these claims is respectfully solicited, as is an indication that the above-referenced application has been passed for issuance. If any issues preventing allowance of the above-referenced application remain which might be resolved by way of a telephone conference, the Office is kindly invited to contact the undersigned attorney.

Respectfully submitted,

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